COMMENT ON GALVEZ-FERNANDEZ ET AL.

Urinary Zinc and Incident Type 2 Diabetes: Prospective Evidence From the Strong Heart Study. Diabetes Care 2022;45:2561–2569

Jingli Yang,[1,2] Juwel Rana,[3,4] and Aimin Yang[5]

Diabetes Care 2023;46:e108 | https://doi.org/10.2337/dc22-2140

We read with great interest the article by Galvez-Fernandez et al. (1) about the association of urinary zinc (UZn) (single exposure) with the risk of type 2 diabetes mellitus (T2DM) among 1,339 adults in the Strong Heart Study (SHS) and 1,905 family members of SHS participants in the Strong Heart Family Study (SHFS). The authors reported that higher UZn levels were statistically significantly associated with increased T2DM risk in the SHS cohort but not in the SHFS cohort. In the sensitivity analyses, the authors evaluated the association of UZn with T2DM risk by adjusting for urinary arsenic (UAs) and selenium (USe) levels using the conventional regression models. However, this study did not report details on the interactions with important predictors, levels of metal concentrations and their correlations, and explanations for their possible influence, although the combined effects of UZn, UAs, and USe on T2DM were not their primary focus.

We would greatly appreciate the response of the authors on the following questions. *1*) Since data on alcohol drinking, waist-to-hip ratio, blood pressure, and lipids were also available and some of them were considered as confounders to evaluate the association between UAs and T2DM in the SHS (2), why the authors did not include these potential confounders in the current study, and what were principles of confounder selection (i.e., directed acyclic graph and change-in-effect estimate)? *2*) The authors provided few explanations of the inconsistent associations of UZn with T2DM risk in the SHS and SHFS. What are the possible explanations for such inconsistent findings, even with larger samples in the SHFS? *3*) The authors observed a stronger association of UZn with T2DM risk in participants with lower BMI in the SHFS but with higher BMI in the SHS. What are the possible explanations for this difference? *4*) Did UZn interact with UAs and USe as well as with HOMA of insulin resistance (HOMA-IR)? *5*) The prevalence of prediabetes was 31.1% in the SHS and 25.4% in the SHFS. Would we reach the same conclusions if the authors estimate the prevalence ratio instead of the odds ratio, since the disease is not rare in the cross-sectional analyses?

Zinc and selenium as trace elements are essential for human health. Arsenic was the first reported toxic metal associated with diabetes (3). Humans are simultaneously exposed to multiple metals that may correlate and interact with each other. Quantification of the health impacts of metal mixtures is a longstanding priority in epidemiologic studies. We should be cautious about adjusting these metals in conventional regression models, which may overlook the complex relationships within metal mixtures and amplify the co-confounding and interaction biases. As authors have available prospective metal mixture data, they can investigate the combined, independent, and dose-response effects on T2DM using recently developed mixture methods (4,5). Furthermore, authors could have analyzed the mediation effect of HOMA-IR or BMI or both to decompose the controlled direct effect and pure indirect effect of UZn or a metal mixture on T2DM risk. Controlled direct effect will inform the true effect of UZn independent of the potential mediation or interaction effect of BMI and HOMA-IR.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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[1]*College of Earth and Environmental Sciences, Lanzhou University, Lanzhou, China*
[2]*School of Public Health and Social Work, Queensland University of Technology, Brisbane, Australia*
[3]*Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine and Health Sciences, McGill University, Montreal, Canada*
[4]*Department of Public Health, School of Health and Life Sciences, North South University, Dhaka, Bangladesh*
[5]*Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China*

Corresponding author: Aimin Yang, aiminyang@cuhk.edu.hk